Novel Aldol-Type Cyclocondensation of *O*-Mesyl (Methylsulphonyl) Cyanohydrins. Application to the Stereospecific Synthesis of Branched-chain Sugars

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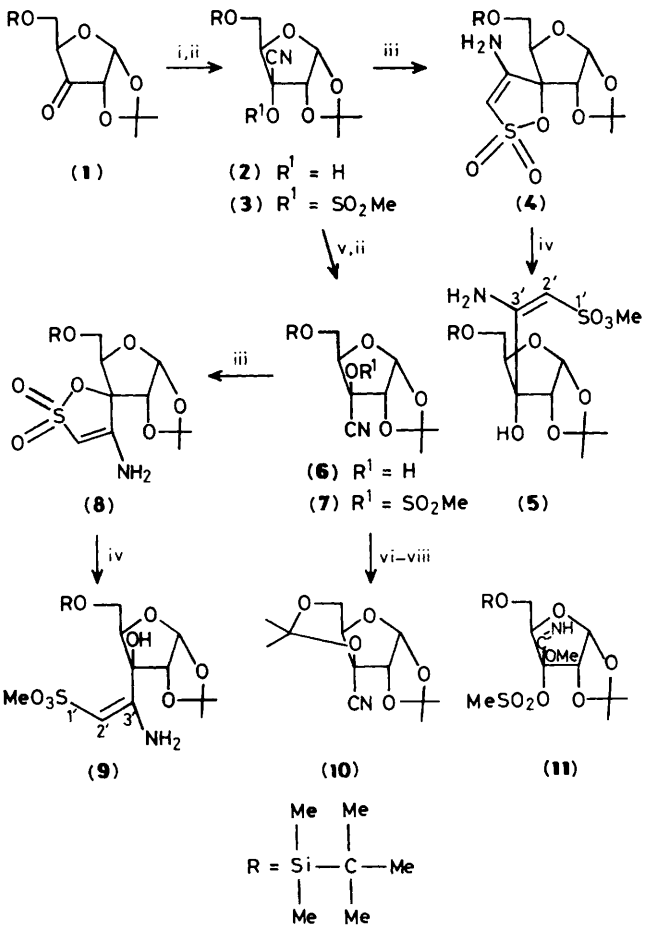
Reaction of *O*-mesylcyanohydrins of furanos-3-uloses with base afforded furanose-3-spiro-5'-[4'-amino-1',2'-oxathiole-2',2'-dioxide] derivatives, which on treatment with MeONa/MeOH gave *C*-[(*E*)-2-(methoxysulphonyl)-1-(amino)-vinyl] branched-chain sugars, having the same configuration as the starting cyanohydrins.

Cyanohydrins and their *O*-substituted derivatives are useful synthetic intermediates, which have been extensively used for the transformation of carbonyl groups into a variety of organic functions.[1,2] Particularly, α-mesyloxynitriles (cyanomesylates) of carbohydrates[3] have been used for the synthesis of rubranitrose, evernitrose, vancosamine, and other components of branched-chain sugar antibiotics.[4] In these synthetic sequences the mesyl group behaves, as expected, as a good leaving group in S_N2 reactions. Here we report a novel, intramolecular aldol-type condensation of cyanomesylates and its application to the stereospecific synthesis of branched-chain sugars, having a highly functionalized *C*-branch.



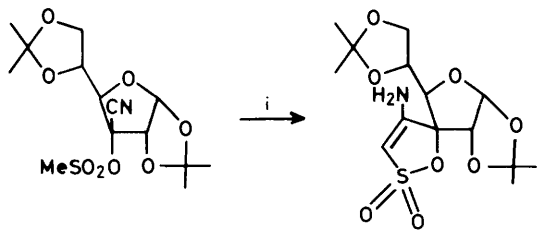
Scheme 1. *Reagents and conditions*: i, NaCN, $NaHCO_3$, Et_2O–H_2O (2:1), room temp.; ii, mesyl chloride, pyridine, 0—4 °C; iii, from (**3**), and (**7**), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), acetonitrile, room temp.; iv, MeONa, MeOH, room temp.; v, from (**2**), DBU, acetonitrile, room temp.; vi, from (**6**), HCl (0.1 M), MeOH, room temp.; vii NaOH, MeOH, room temp.; viii, acetone, 4 Å molecular sieves, TsOH (Ts = Tosyl), $HC(OEt)_3$, room temp.

Reaction of (**1**)[5] with NaCN in diethyl ether/water (2:1) in the presence of $NaHCO_3$ afforded cyanohydrin (**2**) in 94% yield. Compound (**2**) was epimerized to the thermodynamically more stable cyanohydrin (**6**) in 89% yield, by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. The *ribo* and *xylo* stereochemistries of (**2**) and (**6**), respectively, were unequivocally determined as follows. Removal of the 5-*O*-t-butyldimethylsilyl group of (**6**) with HCl (0.1 M), followed by reaction with acetone, *p*-toluenesulphonic acid and triethyl formate, gave (**10**) (61%), m.p. 94—95 °C; $[\alpha]_D$ +53°. A similar treatment of (**2**) did not afford any detectable amount of the 3,5-*O*-isopropylidene derivatives. The *trans*-relationship between the 3-OH and 5-CH_2OH groups in the kinetically controlled cyanohydrin (**2**) is in agreement with the approach of the cyanide ion from the sterically less hindered β-face of ulose (**1**), opposite to the 1,2-*O*-isopropylidene group.

Mesylation of (**2**) and (**6**) with mesyl chloride in pyridine yielded α-mesyloxynitriles (**3**) (80%), m.p. 94—95 °C; $[\alpha]_D$ +39°; and (**7**) (71%) as a syrup; $[\alpha]_D$ +7°, respectively. Treatment of (**3**) and (**7**) with DBU in acetonitrile afforded [1,2-*O*-isopropylidene-5-*O*-(t-butyldimethylsilyl)-α-D-ribofuranose]-3-spiro-5'-[4'-amino-1',2'-oxathiole-2',2'-dioxide], (**4**)†‡ (76%), m.p. 197—198 °C; $[\alpha]_D$ +10°; and the α-D-xylofuranose-3-spiro isomer (**8**),†‡ (71%) m.p. 199—200 °C; $[\alpha]_D$ +2°. The formation of compounds (**4**) and (**8**) can be explained by abstraction of one proton from the mesylate methyl group and nucleophilic attack of the carbanion thus formed at the nitrile carbon atom. The use of other base/solvent systems such as 1 M NaOH/acetonitrile and NaH/dimethoxyethane also afforded spiro derivatives (**4**) and (**8**).

† All products gave satisfactory elemental analyses, i.r., ^{1}H n.m.r., ^{13}C n.m.r., and mass spectra consistent with the assigned structures. *Selected spectroscopic data:* (**4**), i.r. (KBr): (NH_2) 3435, 3200, (C=C–N) 1650 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 90 MHz): 3.95 (m, 2H, H-5), 4.34 (dd, 1H, H-4), 4.62 (d, 1H, $J_{1,2}$ 3.5 Hz, H-2), 4.74 (br.s, 2H, NH_2), 5.57 (s, 1H, H-3'), 5.89 (d, 1H, H-1); (**8**), i.r. (KBr): (NH_2) 3475, 3380, (C=C–N), 1640 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 90 MHz): 3.80 (d, 2H, $J_{4,5}$ 6 Hz, H-5), 4.34 (t, 1H, H-4), 4.59 (d, 1H, $J_{1,2}$ 3.5 Hz, H-2), 4.67 (br.s, 2H, NH_2), 5.41 (s, 1H, H-3'), 5.87 (d, 1H, H-1); (**5**), i.r. (KBr): (NH_2) 3460, 3345, (C=C–N) 1615 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 90 MHz): 3.75 (s, 3H, SO_3CH_3), 3.70—4.10 (m, 3H, H-4, H-5), 4.45 (d, 1H, $J_{1,2}$ 4 Hz, H-2), 4.75 (s, 1H, H-2'), 5.97 (d, 1H, H-1), 6.28 (br.s, 2H, NH_2); (**9**), i.r. (film): (NH_2) 3480, 3360, (C=C–N) 1615 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 90 MHz): 3.76 (s, 3H, SO_3CH_3), 4.10 (m, 3H, H-4, H-5), 4.34 (d, 1H, $J_{1,2}$ 3.5 Hz, H-2), 4.97 (s, 1H, H-2'), 6.00 (d, 1H, H-1), 6.13 (s, 1H, 3-OH), 6.33 (br.s, 2H, NH_2); (**13**), i.r. (KBr); ν (NH_2) 3425, 3330, ν (C=C–N) 1655 cm^{-1}; ^{1}H n.m.r. [$(CD_3)_2SO$, 90 MHz)]: δ 1.23, 1.33, 1.35, 1.55 (4s, 12H, 2 isopropylidene), 3.97, 4.13 (2m, 4H, H-4, H-5, H-6), 4.67 (d, 1H, $J_{1,2}$ 4 Hz, H-2), 5.62 (s, 1H, H-3'), 6.07 (d, 1H, H-1), 6.43 (br.s, 2H, NH_2).

‡ Although the oxathiole ring has priority over the tetrahydrofuran, the numbering of the oxathiole ring has been marked with primes in (**4**), (**8**), and (**13**) in order to keep the same numbering system for the furanose ring in all the compounds of this paper.



(12) (13)

Scheme 2. *Reagents and conditions*: i, DBU, acetonitrile, room temp.

The use of a more nucleophilic base, such as MeONa/MeOH, resulted in nucleophilic attack at the CN group and formation of α-mesyloxyiminoethers, such as (**11**) (61%), $[\alpha]_D$ +50°.

3-*C*-Cyano-1,2 : 5,6-di-*O*-isopropylidene-3-*O*-mesyl-α-D-*allo*-hexofuranose (**12**),[6] on treatment with DBU in acetonitrile also undergoes the above aldol-type cyclocondensation to afford the spiro-derivative (**13**) (66%), m.p. 197 °C (decomp.); $[\alpha]_D$ +18°.

In the above reactions, neither elimination nor substitution of the tertiary 3-*O*-mesyl group was detected. This is in contrast with the reported reactivity of related secondary 3-*O*-sulphonates, such as 1,2 : 5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulphonyl-α-D-glucose and gulose, which by treatment with bases afford the corresponding 3,4-unsaturated sugars by a *trans*-elimination.[7,8] The nucleophilic substitution of secondary 3-sulphonyloxy groups of sugars[9] or the *trans*-elimination to give 2,3-unsaturated furanosyl derivatives has also been reported.[10] Based on these precedents, the basic treatment of (**7**) could conceivably afford elimination of the *trans* related H-4 and 3-*O*-mesyl group. However, this particular mesyl group was a very poor leaving group and did not behave as such under the experimental conditions described.

Reaction of (**4**) and (**8**) with MeONa/MeOH afforded 3-*C*-branched-chain sugars (**5**) (70%), m.p. 67—68 °C; $[\alpha]_D$ −5°; and (**9**) (64%) as a syrup $[\alpha]_D$ +77°.

The overall result of the process described here is the transformation of a cyanide group to a *E*-aminovinylsulphonate derivative with retention of the configuration at the carbon atom in the α-position to the cyano group. Application of this procedure to the readily available cyanohydrins of uloses, stereoselectively affords branched-chain sugars with a highly functionalized *C*-branch. The latter and related compounds which can be obtained from other chiral ketones are potentially useful chiral synthons in view of the variety of asymmetric centres which can be incorporated to the starting ketone and the reactivity of the enamine *C*-branch.

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